combining a mixed population of cells enriched for T cells with at least one first, bispecific, antibody, each antibody, having combining sites specific for a cell surface molecule and at least one product;

exposing the cell population to at least one antigen specifically recognized by a T cell receptor under conditions effective to elicit antigen-specific stimulation of at least one antigen specific T cell;

incubating the combination under conditions and for a time sufficient to allow the cells to secrete the at least one product;

adding at least one label moiety; and

detecting the at least one label moiety.

REMARKS

Claims 1-73 were pending in the present application. Applicants wish to point out that the claim set as originally filed contained an inadvertent error. Claim 26 was omitted, but was inadvertently counted for payment of filing fees. Claims 51-73 are withdrawn from consideration as being drawn to a non-elected invention and new claim 26 has been added. By virtue of this response, claims 1, 14, 23, 31 and 34 have been amended. Accordingly, claims 1-50 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any subject matter of the claims as previously presented. For the Examiner's convenience, an attachment listing the claims presently under consideration, incorporating the current amendments, is attached to this response.

Support for new claim 26 can be found at least at page 31, lines 17-21. Support for the amendments to claims 1, 14, 31 and 34 that recite that the antigen is specifically recognized by a T cell receptor can be found in the specification at least at page 23, lines 12-17 and in the Examples which disclose exposing cells to antigens specifically recognized by a T cell receptor, in particular at page 44, lines 13-19 and page 47, lines 1-7. Accordingly, Applicants respectfully request entry of the amendments to claims.

Concerning compliance with 35 U.S.C. § 112, first paragraph

A. Claims 1-50 stand rejected because the specification allegedly does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The Examiner alleges that the specification is enabling for the claimed method when using high viscosity or gel forming medium but not for the method in the absence of high viscosity or gel forming medium.

Applicants respectfully traverse this rejection and submit that the presently claimed invention is enabled across its full scope. Sufficient teachings have been provided in the application to allow one of ordinary skill in the art to practice the invention as claimed with the exercise of routine experimentation.

The Examiner alleges that the specification does not provide reasonable enablement for methods which do not recite a high viscosity or gel forming medium. Applicants strongly disagree. Applicants submit that the specification teaches methods that distinguish product secreting T cells from non-product secreting T cells and provides several illustrative examples of such methods performed in the absence of high viscosity or gel forming medium.

For example, the specification describes various conditions that are taken into consideration in performing the methods, such as, incubation time and incubation medium. See the specification at page 35, lines 11-26. As disclosed at page 35, lines 15-16, the incubation medium can optionally include a substance that slows diffusion of the product from the producer cell.

The specification at page 44, under Example 1, describes the enrichment of IFN- γ-secreting cells with the magnetic cell separation system, MACS, from peripheral blood mononuclear cells (PBMC) cultured in peptide MI 58-66 from Influenza virus matrix. As disclosed at page 46, lines 1-5, in the peptide stimulated cell population, CD8+ IFN-γ+ cells were enriched up to 40%, in a method performed in the absence of high viscosity or gel forming medium.

The specification at page 47 under Example 2 describes a method for the enrichment of IFN- γ-secreting cells with the magnetic cell separation system, MACS, from peripheral blood mononuclear cells (PBMC) cultured in peptide MI 58-66 from Influenza virus matrix. As described at page 48, lines 15-22, IFN-γ+ secreting CD8+ cells induced by stimulation with the influenza peptide MI 58-66 were significantly enriched above background level, in a method performed in the absence of high viscosity or gel forming medium. Furthermore, all of Examples 4-8 describe methods of the invention performed in the absence of high viscosity or gel forming medium.

The Office Action alleges that Manz et at. establish the need for high viscosity media to practice the instant invention. This clearly has not been demonstrated. In fact, the Examiner appears to inappropriately discount and ignore the teachings of the specification in applying Manz et al. as the basis for this Section 112, first paragraph rejection of claims. M.P.E.P section 2164.01 states that:

> any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Furthermore, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art, without undue experimentation. One of skill in the art following the disclosure of the application would be able to make and use the methods of the invention in the absence of high viscosity or gel forming medium and in the presence of high viscosity or gel forming medium, without any undue experimentation.

In summary, Applicants submit that sufficient teachings have been provided in the specification as filed to allow one of ordinary skill in the art to practice the claimed invention. Therefore, Applicants submit that the application is in full compliance with Section 112, first paragraph and respectfully request withdrawal of this Section 112, first paragraph rejection of claims.

B. Claims 5-7 are rejected under Section 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such as way as to enable one of skill in the art to make and use the invention. The Examiner alleges that claim 1 requires the attachment of the label moiety to the surface of all cells in the population prior to secretion of the product by the activated T cells. The Examiner alleges that the secretion of product does not have any bearing as to whether the label is present on a cell or not and that since all cells are labeled, it would not be possible to separate only those cells which secrete and capture product.

Applicants traverse this rejection of claims.

Applicants respectfully suggest that the Examiner may have misunderstood the invention. In making this rejection, the Examiner states that a "label moiety" must be attached to the cells prior to secretion of the product by the activated T cells (see Office Action at page 3, line 15). This is an incorrect statement. Claim 1, step b) recites modifying the surface of the cells to contain a "capture moiety". Capture moieties are generally known in the art and are described in the specification at least at page 12, lines 21-23 and at page 30, lines 4-29 continuing at page 31, lines 1-21. As disclosed in the specification at page 12, lines 21-23, the capture moiety is specific for the product and includes for example, an antibody or antigen-binding fragment. See the specification at page 30, lines 22-27. A cell that secretes a product becomes "labeled" with that product when the product is captured by the "capture moiety". Captured products can be further labeled with, for example, fluorescent or magnetic labels. See the specification at page 37, under "Cell analysis and cell sorting".

Claim 1 does not require that a "label moiety" (using the Examiner's terminology), a "capture moiety" or a label, such as, for example, a fluorescent or magnetic label, is attached to the surface of all cells prior to exposing the cell population to at least one antigen specifically recognized by a T cell receptor. In claim 1, the step of a) exposing and b) modifying may be performed in any order or simultaneously. The Examiner is incorrect in the statement that all cells are already "labeled" (or are required to be "labeled") prior to exposure to an antigen specifically recognized by a T cell receptor, and therefore, is incorrect in concluding that since

all cells are "labeled", it would not be possible to separate cells based on fluorescent sorting (claim 5) or magnetic sorting (claims 6-7).

Claim 5-7 are fully enabled and Applicants respectfully request withdrawal of the Section 112, first paragraph rejection of claims 5-7.

The claims are novel

A. Claims 1-4, 8, 12, 14-17, and 22-40 stand rejected under Section 102(b) as allegedly anticipated by Manz et al.

Applicants traverse this rejection of claims. Claims 1 and 14 have been amended to recite that cells are exposed to at least one antigen specifically recognized by a T cell receptor under conditions effective to elicit antigen-specific stimulation of at least one antigen-specific T cell. Manz et al. does not teach or suggest antigen-specific stimulation of T-cells. Manz et al. at page 1924 teach that the cell population, that is, murine splenic lymphocytes, were activated *in vitro* with staphylococcal enterotoxin B, a "superantigen". As described in ImmunoBiology: The Immune System in Health and Disease, 2nd edition, by Charles A. Janeway, Garland Publishing Inc, New York at 4:24 and 4:38 (attached hereto as Exhibit A1-A4), staphylococcal enterotoxins are among bacterial "superantigens" and a "superantigen" is an antigen that binds to MHC class II molecules but is not presented as a peptide in the peptide binding groove. Further, stimulation via superantigens is not specific for the pathogen, instead it causes massive production of cytokines by CD_4 T cells. These cytokines have two effects on the host, systemic toxicity and suppression of the adaptive immune response.

In contrast, as taught in the specification at page 23, lines 12-17, a T cell stimulated by an antigen is said to be "antigen specific", i.e., it displays on its cell surface an antigen receptor which specifically recognizes and binds to the antigen in association with a molecule capable of presenting antigen, such as a classical or non-classical MHC molecule or a portion thereof, on an antigen-presenting matrix, for example, a synthetic antigen-presenting matrix or one that is present on the surface of an APC. A T cell which is stimulated by an antigen specifically recognized by the T cell receptor , is specific for the antigen. Therefore, the "superantigen" of

Manz et al. is distinct from the "antigen specifically recognized by a T cell receptor", as is recited in the present claims.

Manz et al. does not teach each and every element of the claimed invention and therefore, as a matter of law, cannot anticipate the claimed invention. Applicants respectfully request withdrawal of the Section 102(b) rejection of claims in view of Manz et al.

B. Claims 1-4 and 8-50 stand rejected as allegedly anticipated by WO 94/09117 by Miltenyi et al. under Section 102(b).

Applicants traverse this rejection of claims.

WO 94/09117 provides teachings regarding selection of cells by secretion product. WO 94/09117 does not provide teachings of T cells exposed to an antigen specifically recognized by a T cell receptor under conditions effective to elicit antigen-specific stimulation of at least one antigen-specific T cell, as is recited in the present claims.

WO 94/09117 does not recite each and every element of the claimed invention and therefore, as a matter of law, cannot anticipate the claimed invention. Applicants respectfully request withdrawal of the Section 102(b) rejection of claims in view of WO 94/09117.

Information Disclosure Statement

The Examiner indicated that only the English Abstract of reference 44 (Peyret et al.) on Applicant's form PTO-1449 filed September 10, 1999 has been considered because the remainder is in French. Submitted concurrently herewith is a Supplemental Information Disclosure Statement, form PTO 1449 and a copy of an English translation of reference 44. Applicants respectfully request that the Examiner initial the form PTO-1449 indicating that the English translation of reference 44 has been considered.

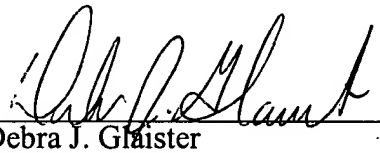
CONCLUSION

Applicants have, by way of the amendments and remarks presented herein, made a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are

respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and/or the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 212302000720. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: February 16, 2001 By: 

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